Attorney Docket No. 26235

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MEIR et al.	Examiner: SAUCIER, Sandra
Serial No.: 10/500,988	Art Unit: 1651
Filed: July 7, 2004	Conf. No.: 3129

For: **METHODS AND DEVICE FOR FREEZING AND THAWING BIOLOGICAL SAMPLES**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Professor Pasquale Patrizio, an American citizen residing at Golden Hill Drive, Guilford, CT, United States, do hereby state and declare as follows:

1. I am currently a Professor of Obstetrics and Gynecology at Yale University, Clinical Practice Director and Director of Yale University Fertility Center. My education and professional experience is provided in the attached *Curriculum Vitae* (Annex A).

2. I have over 15 years of experience in the field of infertility and *in vitro* fertilization (IVF).

3. I am not an employee of IMT Interface Multigrad Technology Ltd.

4. IMT Interface Multigrad Technology has provided me with a copy of the Official Action dated May 6, 2008 in the above captioned application, as well as a copy of the claims for submission responsive to the Official Action, and has requested that I provide my opinion regarding a rejection therein. Specifically, IMT Interface Multigrad Technology has requested that I evaluate the rejection of claims 78, 98-115 and 119-123 under 35 USC § 112, first paragraph as failing to comply with the written description requirement.

5. With regard to the rejection of claims 78, 98-115, and 119-123 under 35 USC § 112, first paragraph as failing to comply with the written description requirement, the Examiner asserts, in part, that the specification does not reasonably provide enablement for the freezing of semen from different species in the absence of cryoprotectant.

6. Having experience in the field of cell and organ implantation and cryopreservation, it is my opinion that the present specification complies with the written description requirement of 35 USC § 112, first paragraph, because the specification as originally filed provides sufficient description for a skilled artisan to make and use a method of freezing at least semen without the necessity of including a cryoprotectant. Additionally, at the time of filing of the present application, a person of ordinary skill in the art would have known that cryopreservation of biological material, and in particular, semen, could be achieved without the absolute inclusion of a cryoprotectant. Taken in view of the knowledge of a person of ordinary skill in the art at the time of filing of the present application, the specification is fully enabling for the present claims. Therefore, it is my opinion that the present specification is enabled for the cryopreservation of at least semen from different species without the absolute need for a cryoprotectant, and no undue experimentation would be required to practice the subject matter of the pending claims.

7. With regard to the description in the present specification, ample written description of freezing semen without the need for a cryoprotectant is given. For example, at page 12, lines 6-30, the specification describes a method for double-freezing preservation of semen comprising: (A) freezing the semen in one or more aliquots; (B) thawing at least one aliquot; (C) dividing said thawed aliquot to smaller aliquots; and (D) freezing at least one of said smaller aliquots. Further, at page 13, lines 1-30 and page 14, lines 1-2 of the specification, an additional double-freezing method is provided that utilizes an isothermal-break method for the freezing or thawing of semen without the need for a cryoprotectant.

8. At the time of filing of the present application, it was generally known to those skilled in the art that freezing a biological sample without a cryoprotectant was possible. The combination of this knowledge and the description of freezing semen without the need for a cryoprotectant, which is disclosed, for example, at page 12, lines 6-30, page 13, lines 1-30 and page 14, lines 1-2 of the originally filed specification, a person of ordinary skill in the art would know how to make and use the presently claimed subject matter, i.e., freeze semen from different species without the absolute need for a cryoprotectant.

9. Accordingly, it is my opinion that the present specification is enabled for the cryopreservation of at least semen from different species without the absolute need for a cryoprotectant, and no undue experimentation would be required to practice the subject matter of the pending claims.

10. I hereby further declare that the statement made herein of my own knowledge is true; and further that this statement was made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 81 of the united states code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dr. Pasquale PATRIZIO, MD, MBE, HCLD

11-3-08

Date

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P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Amir Arav, of 54 Shlomtsiyon Hamalka, Tel-Aviv, State of Israel, do hereby state and declare as follows:

1. I am a co-inventor of the subject matter described in U.S. Patent Application Serial No.:10/500,988, filed July 7, 2004. I am also the sole inventor of the subject matter described in US Patent No. 5,873,254 (hereinafter, "the '254 patent").

2. I have reviewed the Official Action dated May 6, 2008, and understand that claims 78, 98-115 and 119-123 have been rejected under 35 USC § 103(a) as being obvious over the '254 patent alone, and further, in combination with US Patent No. 4,131,200 ("Rinfret") in light of Dayian et al., "Cryopreservation of Human Platelets for Transfusion: A Glycerol-Glucose, Moderate Rate Cooling Procedure," *Cryobiology*, 13, pp. 1-8 (1976) ("Dayian et al.").

3. With regard to the rejection of claims 78, 98-115, and 119-123 under 35 USC § 103(a) as being unpatentable over the '254 patent, the Examiner asserts that the exemplification of the size of the sample in the cited reference is "ABOUT 1 cm x 1 cm x 0.5 mm," and that the "use of the term 'about' in the above exemplification permits a variation of undefined range around this measurement." The Examiner additionally asserts that the mere scaling up of a prior art process is not sufficient to patentably distinguish over the art in the absence of other evidence.

4. The '254 patent describes a device capable of producing a uniform cooling rate of 0.1°C/minute throughout a biological sample. The '254 patent also describes methods for the freezing of semen involving cooling the semen sample from 30°C to an "intermediate temperature" slightly below the lipid phase transition temperature of the semen at a rate slow enough to prevent chilling injury, preferably about 1°C/minute.

5. The presently pending claims are directed to methods for the cryopreservation of semen involving changing the temperature of the semen sample from an initial temperature via an "intermediate temperature" to a final temperature. As recited in the pending claims, the "intermediate temperature" is directly linked to the sample, which has minimal dimensions in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone.

6. It is my belief and understanding that sample size described in the '254 patent is not the same sample size of biological material as presently claimed. Specifically, the description of a sample size in the '254 patent as being "about 1 cm x 1 cm x 0.5 mm" refers to a smaller sample size than the presently claimed sample which has a "minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters." The presently claimed sample size is significantly larger. In cryobiology, the bulk of the sample being frozen is a crucial matter, having great effect on post thaw viability. The larger a sample is the more freezing damage it normally suffers. Unlike small samples, that have almost the same cooling rate throughout their small bulk, more bulky samples suffer damage that is normally due to the poor heat conduction within the sample. This essentially separates the bulky samples to an outer zone (whose cooling rate is affected mainly by the outer environment) and the inner portion (whose cooling rate is affected mainly by the sample's heat transfer properties). This difference in cooling rates and limited inner cooling rate are capable of engendering damaging processes such as recrystallization. The '254 patent did not address the issue of bulky samples and accordingly it does not teach or suggest changing the temperature of the sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature.

7. In this regard, prior to the filing date of the present application, persons having ordinary skill in the art of cryopreservation believed that in order to achieve the best possible viability results during the freezing process, each section of an entire biological sample, e.g., semen, would have essentially the same "ideal" temperature histories, i.e., the time spent at each temperature and cooling rates between temperatures. Accordingly, prior to the time of filing of the present application, skilled artisans, including myself, believed that in order to achieve the best possible viability, while maintaining "ideal" temperature histories during the freezing process, the sample size and volume had to be relatively small, as is described in the '254 patent.

8. However, the presently claimed subject methods exhibit unexpected superior properties because, during temperature change, different temperature histories are exhibited by the outer portion and inner portion of semen samples whose minimal dimensions in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters. For example, when a semen sample is chilled from T_1 to T_2, the outer zone would normally chill quickly from T_1 to T_2 and then remain at T_2, while the inner zone will remain for a longer period of time at T_1 and then chill to T_2. This constitutes different temperature histories for the inner and outer portions of the semen samples, which subsequently would result in different cooling rates for the inner and outer portions, with the outer portion cooling faster than the inner portion.

9. Accordingly, it is my opinion that the '254 patent does not teach or suggest every element of the presently claimed subject, and the presently claimed subject matter exhibits unexpected superior results to the methods previously described. Therefore, the presently claimed subject matter is novel and non-obvious over the '254 patent.

10. With regard to the rejection of claims 78, 98-115, and 119-123 under 35 USC § 103(a) as being unpatentable over the '254 patent in combination with Rinfret in light of Dayian et al., the Examiner asserts that Rinfret describes a bag designed for freezing biological materials such as platelets, and Dayian et al. describes a method for testing the bags, therefore, it would have been

obvious to a person of skill in the art to substitute the controlled freezing method of laterally varying thermal gradients for the uncontrolled platelet freezing method to arrive at the subject matter of the pending claims.

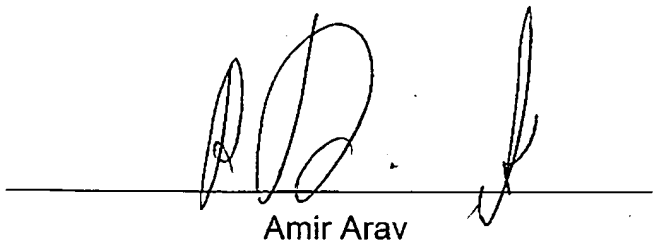
11. Rinfret is directed to a thermoplastic bag for the storage of living cells and a method for freezing, storage and thawing of living cells at cryogenic temperatures.

12. Further, Dayian et al. is directed to a method for platelet cryopreservation using a glycerol-glucose mixture as the cryopreservative agent.

13. As discussed in paragraphs 4 – 10 above, it is my opinion that the '254 patent does not teach or suggest every element of the presently claimed subject, and the presently claimed subject matter exhibits unexpected superior results to the methods previously described.

14. Additionally, neither Rinfret nor Dayian teach or suggest teach or suggest changing the temperature of the sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature. Therefore, the combination of references does not render the presently claimed subject matter obvious.

that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Amir Arav

3/11/08

Date